

*Malarial Fevers
in Relation to their
Parasites.*

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MALARIAL FEVERS IN RELATION
TO THEIR PARASITES

Owing to having practised my profession for some years in Rome and thus frequently been called upon to treat cases of malarial fever, and to the courtesy of my friend ^{Dr} Giuseppe Bastianelli of Santo Spirito Hospital who has afforded me every opportunity of studying the Malarial parasite, I have been led to take "Malarial Fevers in relation to their Parasites" as the subject of my thesis.

It is undoubtedly a subject of practical importance at the present time when the colonisation of tropical countries is so important a feature in the progress of civilization and particularly when the eyes of Europe are turned towards the continent of Africa where malaria prevails. Much theoretical interest also surrounds the disease both in relation to the manner in which the fever is brought about and to the specific means of combatting it ; considerations connected therewith throwing a flood of light upon the general pathology of fevers.

Malarial fever is a disease which as regards geographical distribution girdles the globe, having its greatest intensity in the tropics and becoming much more feeble in the temperate ~~Z~~ones.

In Europe it occurs generally in marshy districts and along the course of rivers ; thus in France

on the ~~West~~ coast between River Adour and River Loire; in Germany, Austria and Russia, along the valley of the Danube. Its chief region however ^{in Europe} is the coast line of the Mediterranean; particularly the coastal line of Sicily and Italy. In Italy it also prevails in the basins of the Po and Serchio, in the plains of Lombardy, and in the Roman Campagna. ~~So~~ also in Africa, Asia, and America, it is met with in its most virulent forms in the tropics, becoming milder in the more temperate climates and with increased altitude, so that it is rarely seen on mountain tops, above an altitude of two thousand feet in temperate climates, and seven thousand in the tropics. Thus its distribution shows it to be a disease of the country and not of the city, existing only where the soil is damp and freely accessible to the air and varying in intensity in direct relation to the temperature whether due to latitude ^{altitude}, or the season of the year.

In Annesley's diseases of India vol, I, it is stated that in India ~~m~~alaria carries off twice as many persons as all other epidemics put together. Sir Joseph Fayrer and other authorities have said that it is the cause of half the deaths throughout the world. From the beginning of the Christian era the parasitic nature of ~~m~~alaria has been suspected, as may be gathered from the writings of Columellus about 45, A.D. Marchiafava and Bignami in the "Poli~~o~~clinico" 1894, fasc 3,

quote Rasori and Bassi as having in the beginning of this century affirmed that " Intermittent fevers were produced by parasites and that the paroxysms depended upon the act of their reproduction and followed each other more or less quickly according to the diversity of the species. "

In 1866 Salisbury of Ohio announced his discovery of a special *Alga* (*Palmella gemiasma*) as the cause of intermittent fevers in the valleys of the Ohio and Mississippi . In 1879 Klebs and Tommasi-Crudeli described the " *Bacillus Malariae* " and had numerous supporters , Marchiafava amongst others (See "Practitioner" November 1880, page 321). So strongly was this *Bacillus* (which is found in soil, water and air of malarious localities) believed to be the true cause of *Malaria*, that Laveran's discovery of the *Plasmodium Malariae* in the blood, was for some years treated with great scepticism .

In 1880 November 23rd to the Académie de Médecine, Paris. Dr. A. Laveran, announced the discovery of the malarial parasite in the blood.

In 1881 Oct 24th, to the Académie des Sciences, he described the appearance of the parasite.

The zoological position of the parasite cannot certainly be ascertained until its whole life cycle is known. So far several organisms have been described greatly resembling the haematozoon but all have

failed by inoculation to convey the disease.

In 1887, Maurel, " Recherches microscopique sur l'étiologie du paludisme ". Paris/202-204, has described amoeboid bodies in vegetable infusion much resembling the amoeba of the blood, but without pigment. In 1890 March, "Riforma Medica". Grassi and Feletti. " Sui parassiti della Malaria " announced their discovery in the soil ; and upon keeping pigeons a few feet from the ground they found them after some days in the nasal cavities of the pigeons. And nine days later semilunar bodies were found in the pigeons' blood. Such observations however lose their value from having been made in a malarial country.

In 1896 Surgeon Major Patrick Hehir M.D. "The Haematozoon of Malaria and its Discovery in Water and Soil", 1896" claims to have discovered an organism resembling the haematozoon in every respect. This however will require further confirmation.

The ~~haematozoon~~ is now recognized to be one of the Protozoa, classified as Haemosporida, and distinguished by the names of Haemoproteus in Amphibians or Reptilia, Haemogregarinidae in birds, and Plasmodia in man.

Mannaberg, (The new Sydenham Society Vol CL) classifies the plasmodia as follows :

1. Malarial parasites with spore formation without the formation of "syzygies"(that is without crescents)

(a) The quartan parasite.

(b) Tertian parasite,

2. Malarial parasites with spore formation, with the formation of syzygies (i.e, with crescents).

(a) The pigmented quotidian parasites.

(b) The unpigmented quotidian parasites.

(c) The malignant tertian parasite.

In 1884, Laveran, (see New Sydenham Society, Vol CXLVI page 82) says " I arrived at the conclusion that the different forms in which the haematozoon of paludism presents itself belong to one and the same polymorphic parasite ; since then I have always upheld this opinion. "

The Italian school believes in the plurality of the parasite and in this they are supported by the results of their inoculation experiments.

In 1895 Di Mattei grouped together several of these experiments (see "Contributo allo studio dell' infezione malaria sperimentale. Arch. per le Scienze Mediche 1895). One cubic centimetre of infected blood was injected, and in 10 to 15 days, a period corresponding to the incubation period, the fever was observed :

Seven tertians were reproduced as tertian single or double, (Antolisei, Angelini. Boix, Bacelli,).

Six quartans were reproduced as quartan, simple, double, or triple (Gualdi, Antolosei, Di Mattei,

Calandruccio Bacelli)

Four irregulars with crescents were reproduced as irregulars with crescents (Gualdi & Antolisei, Di Mattei, Calandruccio). I think these experiments being positive in their results and performed by such careful investigators go far to prove that the various parasites belong to distinct species each having its own biological cycle which does not change. Much of the confusion and doubt which has arisen in regard to this question was probably in cases of mixed infection, where more than one species existed in the patient at one time.

In order to examine the blood in a patient suffering from malaria, prick the finger or lobe of the ear, first wiping with ether to remove any grease or fat. Touch the top of the drop of blood with a cover glass, place the cover glass on the slide and press gently and evenly so that the drop may spread out uniformly between the two glasses. Use a 1/12 homogeneous immersion lens, and N° 4 ocular with Abbé condenser. For accurate study of the structure of the parasite, dried coloured preparations are necessary. Double staining with methylene blue ^{and} eosin are especially useful, giving the blood corpuscles a rose, and the parasites and leucocytes a blue tinge.

The discovery of Laveran has been confirmed by Councilman, Osler, Sternberg, James, Metschnikoff,

Danilewsky, Sacharoff, Barotschewitsch, Khenginsky, Vandyke, Carter, Evans, Plehn, Mannaberg, Bamberger, Quincke and others : also by many general practioners of medecine in tropical climates.

The parasite in its earliest development is a unicellular living organism, transparent, hyaline and unpigmented ; in the fresh state no definite signs of a nucleus can be observed . If stained with methylene blue one can distinguish a deeply coloured ectoplasm and a more ^{lightly} ~~plainly~~ stained endoplasm with a deeply stained point between the ecto-and endoplasm. Most observers interpret the lightly coloured area as the nucleus and the stained dot as the nucleolus or chromatin substance. Bastianelli and Bignami in a paper read before the International Medical Congress in Rome 1894, stated that in the summer-autumn parasites they could not distinguish any body having all the characteristics of a nucleus.

The young parasites look like pale specks resting upon or in the substance of the red blood corpuscles. They are stated by Laveran and Mannaberg to be epicorpuscular in relation to the red blood corpuscle. Mannaberg advises in order to see this, to use an open Abbé and oblique illumination, with concave mirror. Even with this precaution they have always seemed to me to be endocorpuscular and this is the opinion of Marchiafava ; it is quite possible that they may rest for a time on the surface of the corpuscle before they work their way into its substance. There is

usually only one parasite in a red blood corpuscle and when first observed it is about one micro-millimetre in diameter. It gradually grows varying in its ultimate size according to the variety of parasite, until it occupies from a half to the whole corpuscle. The red blood corpuscle is observed to become changed in colour and appearance owing to the parasite absorbing and digesting the haemoglobin. Pigment appears in the body of the parasite as a fine dust or as coarse granules changing more or less rapidly their position in the organism until maturity of the parasite is reached, when the pigment congregates in one part of the body of the parasite, usually in the centre ; then delicate radiating lines pass to the periphery, dividing the body into from six to twenty divisions, each of which divisions becomes a spore and breaks away into the liquor sanguinis. The pigment which remains, diffuses itself in the liquor sanguinis and is taken up by the leucocytes. The crescentic bodies of Laveran, or semilunar shaped bodies, are found in cases of summer-autumn or "intense" fever about seven or eight days after the commencement of the fever. They are fusiform, slightly built, refractile, 8 to 10 micro-millimetres in length and 2 to 3 in breadth. They are endoglobular and the fine outline of the corpuscle can be seen extending between the two horns on the concave side. They contain pigment usually very dark,

quiescent, and centrally situated.

There is a condensation of the external part of the body described by many observers as a double outline due to the presence of a membrane. Laveran (*L'aetiologie du Paludisme*, Revue Scientifique, Paris 1894) states that they are encysted bodies in the red blood corpuscles, and that the existence of a cystic membrane is undoubted.

There is considerable difference of opinion both as to their origin and significance. According to Canalis (Arch. Ital. di Biol., 1890 XIII 262) they represent a more resistant form of the summer-autumn parasite; a form with a cycle of development longer than that of the smaller variety from which however they are directly derived.

According to Mannaberg (New Sydenham Society vol CL, London 1894), they are formed by a conjugation of two of the summer-autumn amoebae. As to the significance of the crescents there have been many conjectures, a few of which I must refer to. Canalis (see "Studii sull' infezione malarica". Giornale medico dell'escercito e della marina, December 1889 : 1358) maintains that the crescents are sporulating forms having definite relation to the paroxysm, and that after sporulation we have again the small hyaline, amoeboid bodies. He regards their presence in the blood as a " constant menace of further paroxysms "

which occur at long intervals of ten, twelve or fifteen days. Thus the presence of these bodies would account for the frequency of recurrence in the summer-autumn fevers.

Bignami and Bastianelli maintain that these forms do not sporulate owing to want of opportunity to do so ; and as I think several English observers have not clearly understood the position of the above authors in regard to this question I shall here quote a portion of their paper read at the International Congress of Rome 1894. (see "Sur le structure de parasites des fièvres estivo-autumnales)" . It is known that two developmental cycles have been demonstrated to exist for numerous unicellular parasites, particularly the Coccidia : the one is completed exclusively during life in the parasitical condition, the other when the parasite has already lived as such for a series of generations : it is represented by forms which cannot complete their development except in the outer world or in the tissues of another animal . If then forms of the second cycle do not escape from the animal in which they are formed they remain sterile and after a certain time they degenerate and die. Well, it appears likely that the malarial parasites, which are developed in shut cavities and cannot reach the outer world, may show a phase of their life which represents a rudiment of this second cycle, which they

are unable to complete. According to this idea the crescents would represent this phase ; an abortive sterile phase of the cycle which in other allied parasites is completed outside the organism. "

Thus it is that Bastianelli and Bignami have considered the crescent a deviate and degenerate form which does not go on to reproduction, because it cannot escape from the body. Of course when it is demonstrated that the crescents do leave the body and continue their development the position of these authors will no longer be tenable.

Dr Manson (see Goulstonian Lectures, British Medical Journal March 14th, 21. 28) combats the view that these forms are degenerate and suggests that they obtain their opportunity for further development in the body of the mosquito by the ~~presence~~^{cess} of flagellation. I feel that there is much to recommend Manson's view, for that we should find such constant and abundant forms so well defined to be useless, is contrary to the theory of evolution, which theory excludes all useless forms.

The flagellate bodies were first described by Laveran and were believed by him to represent the highest stage of development of the ~~malarial~~^{parasite}. They emanate from large passive pigmented forms of the tertian parasite, less frequently from the quartan, forms that have not gone on to segmentation, and also from the crescents after they have become transformed into

ovoid or spherical

ovoid or spherical forms. There may be three or four flagella attached to one such body extending from it like tentacles. They are 20 to 30 millimetres in length, very delicate and have active lashing movements. They break off from the central body and move off with a spirillum-like movement. They are only seen some fifteen or twenty minutes after the blood is drawn from the body. By most of the Italian school they are believed to be agony forms of dying parasites. Laveran, Mannaberg, ~~Cornarado~~^{on}, Manson and Ross, on the other hand believe that the flagella represent the first steps of a cycle of existence outside of the human body. Ross (see "^{ser}Observations on a Condition necessary to the Transformation of the Malaria Crescent ") has shown by the simple experiment of drawing the blood surrounded by vaseline, that the death of the crescent can take place without the formation of flagella simply by shrivelling at its ends. He believes that a change in the density of the blood is the stimulus required to induce the evolution of the flagella.

The appearance of the flagella with their active, lashing movements certainly gives one the impression of life. In this relation we may bear in mind that the tendency of the Italian school was even to view the parasite of Laveran as a retrograde change in the red blood corpuscle, as urged by Marchiafava,

Celli and Crudelli at the Congress of Copenhagen 1884
 (see Marchiafava and Celli "Sulle alterazione dei
malaria" - *Reale Accademia dei Lincei, Roma*). Besides these
 globuli rossi nell' infezione di parasitic forms there
 are found in malarial blood immobile, hyaline, pigment-
 ed, deformed and vacuolate bodies which are cadaveric
 forms of those described : also pigmented leucocytes
 which have absorbed the free melanin from the liquor
 sanguinis : also, but much more rarely, leucocytes with
 parasites in various stages, but immobile.

Golgi's researches demonstrated the connection
 between the life cycle of the parasite and the clinical
 cause of the disease, describing them in all their
 stages in the quartan and tertian fevers. He showed
 how the parasites grew from non pigmented to pigmented,
 gradually increasing in size and becoming mature just
 a little before the commencement of the next attack
 of fever. He also proved that the parasites were not
 all of one species, but that there are different spe-
 cies corresponding to different clinical types. He
 stated

(1) That only amoeboid forms in different stages
 of development, pigmented and segmented forms ^{are} found
 associated with the milder tertian and quartan fevers,
 rarely flagella and never semilunars.

(2) That the parasite producing the tertian fever
 is both biologically and morphologically different from
 that causing the quartan fever.

As a corollary we must admit three varieties
 of parasites, tertian, quartan and the semilunar forms.

These observations of Golgi's (see Golgi "Sull' infezione malarica Arch. delle Scienze Mediche Vol X 1886) have been fully confirmed by other observers and by the inoculation experiments already mentioned in this paper.

As the tertian and quartan fevers have been observed to invariably commence in spring ; they have been termed the winter-spring fevers ; the semilunar forms occurring chiefly in summer are known as the summer-autumn group of fevers. This classification applies fairly well to temperate climates such as Italy ; but in the tropics the summer-autumn exist all the year round.

Winter-Spring Fevers.

Quartan Fever is associated with the life-cycle of a parasite which takes 72 hours to develop; hence the paroxysm occurs every fourth day.

Should there be two generations of parasites then the paroxysms occur upon two successive days followed by a day of intermission. (Double Quartan,) If three generations are present we have a quotidian fever, (Triple Quartan). The period of incubation varies as shown by inoculation experiments according to the number of parasites received into the system at one time from 11 to 15 days, average 13 days.

During the period of incubation there is frequently headache and nerve disturbances so that the

patient complains of feeling ill before the paroxysm has commenced. If shortly before the paroxysm the blood be examined, mature sporulating forms may be seen occupying almost a whole red blood corpuscle, likened by Golgi to a daisy ; the centre of the parasite is occupied by a mass of fine pigment granules ; from this fine radiating lines run to the circumference, dividing the parasite into from six to ten segments. The temperature gradually rises for a few hours, headache increases, nausea and vomiting may be present and then with severe shivering is ushered in the cold stage of the fever. At this time the skin is blue, the headache is intense, there is a small quick pulse, and the temperature rapidly rises to 105°F or 106°F. This lasts from a quarter of an hour to two hours, when we have the hot stage with a complete change in the character of the skin, which instead of being cold and pinched becomes flushed and reddened, the pulse full and bounding, head throbbing, great thirst. These symptoms last for three or four hours, the temperature continuing high and only falling with the sweating stage, which brings down the temperature giving great relief to the headache and all the other symptoms. The patient falls into an easy sleep, not only the skin but the kidneys are also very active, an acid high coloured urine of sp. gr. 1020 - 25 being voided.

The paroxysm lasts for 10 to 12 hours. The spleen is always enlarged. During the whole course of the paroxysm sporulation continues and on ~~the~~ examination of the blood the segmented forms are seen breaking up and leaving disintegrated masses of pigment floating in the liquor sanguinis until taken up by a phagocyte. The leucocytes which perform this function may be seen most abundantly during the hot stages of the fever as white blood corpuscles and large mononucleated cells with a fine granular protoplasm, which are of spleno-medullary origin. The progress of phagocytosis although observed in the general circulation goes on even more actively in the spleen, liver, and medulla of the bones. The phagocytes enclose not only blocks of pigment but adult forms of the parasite ready to sporulate, and even blood corpuscles, which have undergone alteration by reason of the parasite.

Besides the segmented forms may be seen large pigmented adult parasites not having yet sporulated. Towards the end of the paroxysm tiny hyaline specks are visible upon the red blood corpuscles, which are the young parasites. Free spores may be seen floating in the liquor sanguinis, but it is very difficult to feel sure that they are not blood plates. Ten or twelve hours after the termination of the paroxysm the hyaline specks are observed to have grown, to have a slight amoeboid movement, and to be either lying upon

or buried in the substance of the red blood corpuscles. It is at this stage of development that vacu^uoles are so apt to be mistaken for parasites. They are due to a contraction of the substance of the haemoglobin, and thus the colourless stroma of the corpuscle appears as a bright spot, more brilliant than a parasite, with a more distinct boundary not merging into the substance of the corpuscle as does the parasite. Twenty four hours after the paroxysm the parasite has grown to about about 1/5th the size of the red blood corpuscle; it shows slow amoeboid movement and contains a few granules of pigment through its substance.

Sixty hours after, the parasite occupies almost the entire red blood corpuscle, only a very faint rim being left with signs of commencing sporulation, concentration of pigment and radiation having taken place.

Tertian Fever, is dependent upon a parasite which completes its entire cycle in 48 hours and thus a paroxysm, which, as in the quartan fever, commences with the maturation and sporulation of a generation of parasites, occurs every second day. If two generations be present at the same time, there is a daily paroxysm - double tertian - a quotidian fever. The period of incubation is shorter than that of quartan fever, being from 6 to 12 days, averaging 10 days. The paroxysm much resembles that of quartan fever lasting from 10 to 12 hours with a cold, hot, and sweating

stage. The parasite possesses several characteristic distinctions which distinguishes it from the quartan parasite. Its evolutionary cycle is 48 hours, in place of 72, it is more delicate, fainter, with finer pigment granules, which are lighter in colour, and the ameboid movement is much more rapid. The effect upon the red blood corpuscle is also different in the tertian, the invaded globules become rapidly decolourized and expand, becoming larger than the normal corpuscle ; whereas in the case of the quartan the corpuscle tends to shrivel. The tertian parasite also differs in method of segmentation, and the spores are more numerous than in the quartan. The pigment collects in the centre of the haemocyte in a block and the peripheral part of the parasite takes the form of a ring which divides into 15 - 20 spores, first oval then globular, and arranged like a crown-resembling a sun flower according to Golgi. These mild fevers (the quartan and tertian) are rare in hot climates ; they are very amenable to quinine, and even without any therapeutic agent the parasite dies out in the course of a fortnight. They leave behind them a very marked anaemic condition owing to the destruction of the red blood corpuscles known as post-malarial anaemia or cachexia, This however is mild as compared with the same condition arising after the summer-autumn fevers.

The second group of fevers are much more severe

in type than the quartan and tertian and are always associated with the crescents of Laveran, - They have been termed nemittent, continued or irregular, and as in temperate climates they usually occur towards the end of summer, they have been grouped by Marchiafava as "Aestivo-autumnal Fevers."

The parasites of this group are more difficult to study, as part of the evolution in their development takes place in the internal organs, that is the process of sporulation. Owing I believe to mechanical causes in the circulatory organs of the individuals attacked the accumulation of sporulating bodies takes place more largely in one organ than another, and thus gives rise to a train of symptoms in relation to that organ : thus, when the brain is the organ chiefly so affected we have the fever distinguished as Comatose; should it be the stomach, intestines or the glands, which are the chief site of the sporulating parasite, then the fever is Gastro-intestinal or Algid. The parasites of this group are smaller in size than those of the quartan and tertian fevers ; they frequently take an annular form rarely seen in the others and the pigment which they contain is finer, scarcer, and not so mobile.

They are much more virulent^e than are the tertian and quartan parasites and have a markedly poisonous effect upon their hosts, the red blood corpuscles

causing them to shrivel up and change colour to a brassy tint and thus in Italy giving ^{the confusioles} the name of "ottonati."

As regards their reproduction they are exceedingly active, the process of sporulation taking place almost entirely in the internal organs and not in the peripheral circulation ; there may be several generations in the blood at the same time and it is to this that is due the frequent irregularity of the fever, the various generations maturing and sporulating at different times.

In Rome they commence about the end of June or beginning of July and run on to October. They are distinguished by Marchiafava and Bignami (New Sydenham Society. London. Volume CL) as dependant upon ~~two~~ varieties of parasites, quotidian and tertian. These however so closely resemble each other in many ways that other observers do not believe in there being two varieties properly so called, but only one parasite which may present appreciable differences of form in relation to the duration of its life-cycle, which is of a variable length.

Mannaberg, who agrees with Marchiafava and Bignami apparently, admits certainly the existence of a clinical quotidian and tertian type of intense malaria, but does not believe that it is yet settled whether the parasites which give rise to quotidian are different from those which cause tertian, because

even in coloured preparations the details of the structure of the supposed two varieties appear identical. He admits instead that a quotidian exists which is due to a non-pigmented variety, in which sporulation takes place as it were prematurely before pigmentation can occur. That this may happen in the fevers of malaria intensa had been observed by Marchiafava and Celli in their first researches ; but they are very rare cases and when such forms of sporulation are observed there are also present pigmented forms. Marchiafava and Bignami with reason declare that such division must be rejected until cases of malarial ~~infection~~ infection without pigmented forms are found, and none should be accepted without microscopic examination of the viscera usually most melanosed. Thayer and Hewetson (John Hopkins Hospital Reports Vol 1895) believe that there is only one type with considerable variations in its life cycle as to duration ; they do not even admit two clinical types.

Marchiafava and Bignami do not themselves regard the matter as settled and admit the great resemblance between the two varieties, and declare the differential diagnosis to be very difficult and only possible in the adult forms especially during apyrexia. They admit that it is possible to explain the differences in the two varieties as due to differences in the length of the life-cycle, but point out that the two types are clinically pretty distinct, and have a certain stability by repeating themselves in subsequent relapses and recurrences. They have never seen clinical intermediate forms which might not be referred to one of the two described types .

Personally I have very little hesitation in following Marchiafava and Bignami, knowing the large amount of material they have to enable them to form an opinion, and also being impressed with the care and skill which they bring to bear upon the question.

Quotidian Fever is distinguished by more or less regular daily paroxysms characterized by a gradual rise of temperature extending over a period of six to twelve hours , reaching 104 ° F to 100° F, frequently

commencing without rigor or cold stage. The spleen is enlarged and tender. The patient feels very ill and complains of intense headache, muscular pains in the back and in the calves of the legs, a general feeling of depression and loss of appetite. There is a thick white fur on the tongue, pallor of the face, frequent diarrhoea and a typhoid appearance. The paroxysms gradually and steadily become weaker: but relapses are frequent, occurring three or four days after termination of the fever, a ^{period} ~~fever~~ corresponding to the incubation period of this fever. Recurrences also occur at much later periods and may be due to the crescents. The fever frequently becomes subcontinued owing to prolongation of the paroxysm.

Examination of the blood of the finger at the commencement of the paroxysm discovers adult forms of the quotidian parasite about $\frac{1}{4}$ to $\frac{1}{5}$ the size of the infected red blood corpuscle, which is itself shrunken and copper-coloured. Pigment is collected in the middle of the parasite, which it may be seen breaking up into spores. It is rare however for fission to take place in the peripheral circulation. During the paroxysm young parasites can be seen either as actively moving pale spheroidal or irregular specks swimming in the substance of the red blood corpuscle, or as quiescent whitish ringlets with a reddish centre. During the intermission these bodies gradually acquire pig-

ment increasing in size until they become adult parasites and thus run their cycle in twenty four hours. Grassi and Feletti, also Mannaberg, describe an unpigmented quotidian parasite much resembling the above but running its whole course without acquiring pigment. After the fever has repeated itself for several days crescentic bodies can usually be seen. Summer-Autumn or Malignant Tertian is more difficult to study owing to the number of groups or generations of the parasite present in the blood at the same time, to the fact that sporulation takes place in the spleen and internal organs, and above all owing to the uncertainty as to whether it is due to a distinct parasite or to a modification of the parasite already described as quotidian.

Thayer and Hewetson, (John Hopkins Hospital Reports Vol V, 1895, page 119) in their analysis of 189 cases, describe 100 of them as quotidian and some 15 or so as tertian in character and therefore they believe that so far only one parasite of aestivo-autumnal infection can be recognized, and that the irregularity in the febrile manifestations is due chiefly to the tendency on the part of the parasite to irregularities in the length of its cycle of development . I think from a study of the cases described by Thayer and Hewetson and also those of Marchiafava, that the pseudocrisis described by the latter in the thermic curve has been looked upon by the former as

a true intermission and thus these observers have described as a quotidian fever what Marchiafava and Bignami maintain to be a tertian with ^{prolonged} pseudoërisis .

The paroxysm as described by Marchiafava and Bignami is a very long one exceeding 24 hours, beginning with an abrupt rise of 104° F or more, then falling and oscillating between 100° F and 102° F (the pseudocrisis) then shooting up to 105° F or 106° F (the precritical elevation,) before gradually falling to normal.

The subjective symptoms are exceedingly varied but there is always present a feeling of great depression, severe headache, and frequently abdominal pains with diarrhoea. The symptoms abate so little during the period of apyrexia that the patients think they are suffering from a continuous fever. On examination of the blood at the beginning of the paroxysm the adult form of the parasite can be seen occupying about half a red blood corpuscle, which is shrivelled and of coppery colour. It is round or ovoid in shape with granules of dark pigment gathered in the centre, or eccentric. The granules are very fine and are in motion. It is at this stage of development that it can be observed to some extent to differ from the quotidian parasite in that it is larger and exhibits more active amoeboid movement . During the first five or six hours of the paroxysm these adult forms become exceedingly scanty or altogether absent, as when they are ripe for fission they remain in the

internal visceral organs and there sporulate . And thus thus
 thus there may be a period when no parasite can be
 observed in the finger-blood. Nine or ten hours after
 the commencement of the paroxysm the adult forms may
 still be seen and indeed throughout the whole parox-
 ysm the adult forms are usually present, pointing
 to the probability that there are groups of parasites
 of different ages in the blood, that throughout the
 paroxysm they come to their maturity, and that the
 sporulation of each group corresponds with an increase
-thus accounting for the oscillations of temperature
 of temperature during the pseudocrisis; and the de-
 layed sporulation of the last group causing the pre-
 critical elevation.

Coincident with the adult forms are the young
 parasites, about $\frac{1}{4}$ th the size of the red blood corpus-
 cle either as exceedingly active amoeboid forms ^{pushing} pseu-
 dopodia into the substance of the red blood corpuscle;
 or they may be motionless , and are then either annu-
 lar of a shining appearance, or discoid with a wavy
 outline. Toward the end of the paroxysm they are
 about one third of the size of the red blood corpuscle
 containing fine granules of pigment, generally arrang-
 ed on the edge, but sometimes scattered throughout
 the protoplasm of the parasite. During apyrexia they
 increase slightly in size and become more pigmented.
 This fever usually subsides in about a week or ten
 days, and about this time the crescent-shaped bodies

of Laveran appear. *As* in the quotidian fever relapses and recurrences frequently occur.

Owing to the sporulation taking place in the internal organs, the brain, lungs, spleen, osseous marrow, liver and intestines, the capillaries of these organs become blocked with amoebiferous red blood corpuscles and accordingly give rise to symptoms from their presence there. Thus particularly in the brain enormous numbers of amoebiferous red blood corpuscles accumulate in the capillaries giving rise to delirium or coma which may last from 18 to 24 hours or may result in death. There may be partial recovery with permanent injury such as aphasia or hemiplegia : in such cases Bastianelli has demonstrated that there are punctiform haemorrhages in the white substance of the brain due to diapedesis taking place. Such are the comatose cases already mentioned. Again we may have the mucous membrane of the gastro-intestinal tract engorged with parasites, ulcerating and necrosed, and giving rise to diarrhoea and great prostration. Such cases termed algid have naturally been frequently confounded with typhoid fever : the great enlargement of the spleen further tending to increase this confusion. Here the value of blood examination for the parasite can be clearly demonstrated as the only certain means of distinguishing this as a malarial fever and no longer a typho-malarial, as hitherto classified. In these cases besides the amoeboid forms the crescent shapes

are particularly abundant.

The enlargement of the spleen is due to the accumulation of changed red blood corpuscles, parasites, endothelial cells, and necrotic debris. In the tropics after two or three attacks of fever haemoglobin^{uria} is frequent ; in Africa so much so that it receives the special name of "blackwater " fever. This condition is seldom or ever observed in central Italy ; but several cases have been recorded in Sicily. The urine is albuminous, red, brownish, smoky or black in colour, containing pigmented urates, granules of pigment, and epithelium. The spectroscope shows three absorption bands due to methaemoglobin^h, sometimes the two absorption bands of oxyhaemoglobin.

G.Bastianelli (Le emoglobmurie di Malaria Fasc. XI degli "Annali di Medicina Navale" Anno 11) shows that the haemoglobin^huria coincides in time with the process of sporulation in a group of parasites, and to a fresh invasion of the young forms produced, into the red blood corpuscles.

F.Plehn, (Das Schwarzwasserfieber der Afrikanischen Westküste, Deutsche Medicinische Wochenschrift 1895) states that the condition depends largely upon individual predisposition, as many individuals suffer for years from grave fevers and relapses without having haematuria, whereas others suffer shortly after they arrive in Africa. He also thinks that great emotions

fatigues and colds predispose to it.

Tomaselli ("La intossicazione clinica o febbre itteroematurica da chinino") states that it is due to the administration of quinine and that where quinine is not given you do not find haemoglobinuria. This point is so far by no means settled although the same view is to some extent supported by Dr Albert Plehn (Beiträge zur Kenntniss von Verlauf und Behandlung der tropischen Malaria in Kamerun.)

I think in the present state of the question, there being considerable difference of opinion as to whether quinine does or does not tend to produce haemoglobinuria, a serious condition, that quinine in such cases should be administered intelligently and with caution, the ground of administration being the ascertained presence of the parasite in the blood of the individual.

Severe malaria always leaves a cachectic condition, due to the destruction of the red blood corpuscles by the parasite. The blood-count shows in severe cases an enormous diminution in the number of the blood corpuscles, even to 1,000,000 per cubic millimetre. The skin is yellowish in colour and there may be an irregular fever with a temperature varying from 102.5° F to 103° F. There are sometimes retinal haemorrhages. The spleen is greatly enlarged, hard and firm.

We have seen that in all the malarial fevers the paroxysm coincides with the process of sporulation in the parasites, and therefore it is reasonable to suppose that some change takes place in the blood at that time, to account for the fever. In every probability some poisonous material present in the spore-forming bodies is eliminated during sporulation and causes irritation of the heat centres. Certain researches point to this. Roque and Lemoine "Recherches sur la toxicite urinaire dans l'impaludisme" state that the urine after a paroxysm acts as a poison to rabbits, and that, passed before the paroxysm is much less poisonous. Queirolo ("Riforma Medica Roma 89 N° 254.) has killed rabbits by injecting the sweat obtained from patients during the sweating stage. The nature of this poison is believed by some to be very similar to that produced by the bacteria which causes septicaemia.

To those who have had practical experience in the treatment of cases of malaria and opportunity for microscopical observation there is but little doubt that the disease is caused by Laveran's parasite. That this knowledge does not obtain in all quarters however is evident from the published work of W. North. upon "Roman Fevers." 1896. This author maintains that the "Chill Theory" or some modification of it is more logical than what he terms the "Germ Theory". He reasons in favour of the Chill Theory, that the fever

prevails only in climates where there are rapid and *great* daily changes of temperature, and further having made a series of thermometric observations as to the atmospheric conditions a few feet above the ground level, and having found that the temperature is more equable at these levels, he maintains that it is on this account that those who take the precaution of sleeping at such levels are less liable to suffer from ~~f~~ fever. If this were a tenable theory and *Malarial fevers* were contracted on account of chill without any other factor being required surely then all who resided in climates where the changes of temperature were rapid and who subjected themselves to chill by sleeping on the ground would sooner or later suffer from malarial fever. This is opposed to general experience and particularly to my experience in Australia where I practised for nearly ten years in a climate very similar to that of central Italy. There I treated many shepherds, labourers, and others who were subject to conditions very similar to workers in the Roman Campagna, living upon a poor diet of tea and damper, and sleeping in tents in the Australian bush; and although they frequently suffered from chills and pneumonia, malarial fever never occurred amongst them, being unknown in that country.

North in contesting the "Parasitic Theory" makes much of Koch's postulate as to cultivation, not

having been fulfilled. It is true that so far all attempts at cultivation outside of the human body have failed, nor is this much to be wondered at when we consider the exceeding delicacy of the organism, so much so that a slight change in the oxygenation of the living medium, the blood in which it thrives, is sufficient to cause its death. This being so we may be obliged to remain satisfied with being able to reproduce the parasite by means of inoculation into healthy subjects. This as already mentioned in this paper has been carried out by many skilled workers and not as suggested by North in malarial localities only, so that the experiment would thus lose its significance; but in localities where malaria is unknown, as in hospitals in the centre of cities. Besides the undoubted evidence which we have of the success of inoculation experiments, we are further aware that the number of cases of fever in which the parasite is not found are now exceedingly few and from my own personal experience I am convinced that they will become fewer; for in cases in which I was unable to detect the parasite, my friend Dr Bastianelli detected them immediately. Thus the presence or supposed absence of the parasites depends largely upon the skill and experience of the observer.

North thinks it extraordinary that the parasite in Sweden should differ from that in Italy, in

being so much less virulent. As we have seen the summer-autumn parasite of Italy actually does differ from the tertian and quartan of Sweden. I may mention that we do not think it extraordinary that the Repetilia of the tropics are more poisonous than those in northern climates.

I admit that the parasitic theory is founded upon the reasoning of "Post hoc ergo propter hoc," *but* ~~and~~ I maintain that when the "hoc" becomes so constant a factor, as is the parasite in malarial fevers, supported by the experience of so many skilled scientists ~~sub~~ such reasoning is highly satisfactory.

I certainly do not think any medical practitioner who has been called upon to treat chills even of the severest kind and also intermittent fevers with their sequelae of the cachexia, discoloured skin, disorganized blood, and organic changes of the spleen and liver can ever for a moment accept the "Chill Theory" of malarial fevers.

As to the means ^{of the conveyance} of malarial infection, there is considerable difference of opinion, owing to the parasite not having been isolated. The fact however that the disease can be transmitted by inoculation suggests the possibility, sometime ago mentioned by Laveran, that insects may by means of their bites insert the poison into the blood.

Dr Martin Clark in a valuable address upon

" Malaria and Acclimatisation " read at a meeting of the Scottish Geographical Society in Edinburgh, April 1892, says that inoculation of the virus by insects may take place from the original source of the poison, from person to person, or by contamination of food and water in which they breed and die. The same author is of opinion that malaria may be imbibed in water owing to its having absorbed the germ passing over its surface, or from the subsoil water passing into wells. This opinion is very generally held by observers through India and by Bacelli of Rome, who states that the disease should be called "Malacqua" as well as "Malaria." The later Italian school do not favour this view, and Marchiafava, Bignami and Bastianelli have experimented by giving individuals water from malarial centres to drink, and have never thus conveyed the disease. This however was not the experience of Laveran and further I think negative experiments of this kind are not very trustworthy, for of course we do not know with certainty that the water was malarial and even if so the chemical constitution of the water may have affected the virus. The belief is almost universal that malaria, (hence the name) may be inhaled in the air, early morning before sunrise, and evening after sunset, being the periods of greatest liability to infection. At these periods the lower strata of air ascend in strong currents and probably carry the parasite with them. Thus in short.

the contagion of malaria enters the system, either through the skin by insect bites, through the digestive tract, or by the respiratory tract. Dr Manson in the Goulstonian Lectures 1896 drew analogy between the life-cycle of the filaria sanguinis hominis and the hamatozoon of malaria in relation to the mosquito as intermediate host. One cannot but be impressed by his arguments, but at the same time it would seem that malaria exists where mosquitos are unknown, particularly in the case of the milder fevers. Dr Manson considers the escape of the parasite by the decomposition of the human host after death as in the highest degree improbable ; he says " Malaria is far from being a fatal disease, the plasmodium like other parasites is not likely to depend on what relatively to the frequency of malarial infection is altogether an exceedingly rare and exceptional occurrence."

I might here suggest that death is not rare and exceptional if we accept a broader distribution of the parasite. In birds and turtles the haematozoon resembles morphologically that in men and it has by no means been proved that they are ^{not} identical. The fact of their not affecting birds similarly to man is probably due to the constitution of the bird and not of the parasite. Thus if the same parasite infests animals other than man, that perish on the ground, there is then constant opportunity of escape for the parasite. The parasite has apparently the power of

remaining dormant in the human system for prolonged periods, as shown by recurrences of the fever ; and it is not unreasonable to suppose that it may retain this power until the death of the host. The breaking out of fever upon making excavations in soil that has not been disturbed for centuries, points to the latent power possessed by the spore, the crescent shaped bright refractile forms which are very abundant in the blood of birds giving one the impression of being exceedingly resistant. The fact of the parasite not having been isolated outside of the human body does not prevent us from recognizing the conditions upon which its activity and virulence depend, namely a porous humid soil with a temperature of over 60° F. This being so, in the counteracting of these conditions lies the general prophylaxis of the disease, that is, to remove the moisture from the soil by drainage, agriculture, or the planting of trees; to prevent the oxygenation of the soil by pavings in towns and growing thick rooted grasses in the country, or by covering with a layer of non-malarial soil. The temperature cannot be altered but the precaution of only working in malarial soils in winter can be taken. It has further been noticed that the malarial contagion does not rise vertically. Of the villages on the hillside of the Pontine marshes, those that stand vertically on the summit of a perpendicular surface such as Norma are

healthy and those on a slope such as Sermoneta are in summer uninhabitable ; even comparatively low altitudes such as twenty or thirty feet prove a protection against the contagion. Thus in the Campagna of Rome the shepherds sleep on the summit of tombs, and in India in trees.

Individual prophylaxis consists in taking a daily dose of from three to five grains of quinine, which may be taken as quinine wine in the morning and in the afternoon. This precaution with that of ordinary hygiene such as warm woollen clothing, avoiding over fatigue, moderation and care in food and drink, will do much to prevent attacks even in the most malarial countries.

In treating the disease all drugs which diminish or arrest the process of oxidation in the blood will tend to destroy the parasite by preventing its nutrition : such drugs as quinine, arsenic, morphia, strychnine, nicotine, alcohol. Quinine however leaves the others far behind as a specific against malaria and is universally used. As Cinchona under the name of Peruvian bark it was used in England upwards of two hundred years ago, especially as a cure for ague. Binz has demonstrated its action and shown that it prevents oxidation in the blood. According to Rossbach it prevents oxidation by causing the oxygen to form a closer combination with the haemoglobin in the red

blood corpuscle and thus preventing the oxygen passing into other substances. As oxygen is a requirement of the parasite to carry on its nutrition and development, the parasite is thus starved.

Golgi has demonstrated that if quinine be given ^{4 or 5 hours} before an attack of quartan or tertian fever the paroxysm is not prevented and indeed the parasites go on to sporulation, but young spores are killed, or as Mannaberg states are "still born" being without a nucleus and powerless to invade another red blood corpuscle. Thus the quinine hinders the nutrition and development but is powerless to prevent the process of fission.

Marchiafava has shown that in the summer-autumn fevers quinine acts with efficacy in all the stages of the amoeba's life except in those where the process of reproduction is completed; and so in these fevers he advises that the paroxysm should not be waited for, but the quinine should be given as soon as possible and in repeated doses every four to six hours.

Quinine may be given in three ways; viz, by the mouth, by hypodermic injection, or by intravenous injection.

The hydrochlorate of quinine is more active than the sulphate.

For the milder quartan and tertian forms it is sufficient to give it by the mouth and one gramme

(that is 15 grains) should be given three to five hours before the paroxysm ; this before three consecutive paroxysms will stamp out the fever. In the milder of the summer-autumn fevers, it may be given by the mouth, 15 grains, repeated in four hours, and then ten grains every twelve hours until the fever is overcome.

In severe cases of the summer-autumn it is better at once to inject hypodermically 15 to 30 ^{ins} grammes, (that is thirty to sixty minims of the following prescription.

Quiniae Hydrochloratis.... $\overline{z} \overline{l} \overline{l}$
 Acidi Hydrochlorici diluti.... $\overline{z} \overline{l}$
 Aquam destillatam ad.... $\overline{z} \overline{l} \overline{v}$

In very severe pernicious cases inject 60 to 90 minims , and then 30 minims every four hours. In comatose cases Bacelli advises intravenous^{ou} injection of the hydrochlorate of quinine in a saline solution.

To prevent relapse an occasional dose of quinine should be given. In Java 1 gramme is given every seventh day.

Plehn found in the fevers of Kamerun that this was too long an interval and used effectively $\frac{1}{2}$ gramme every five days.

The other drugs mentioned are rarely used, but in cases where quinine cannot be given owing to causing dangerous quinine intoxication, morphia would be useful followed by arsenic.